

## REMARKS

Claims 45 and 50-52 have been amended, and new claims 54-62 have been added. Claims 1, 23, 41, 42, 45-48, and 50-62 are pending in the instant application. No new matter has been added as a result of the above-described amendments. The objections and rejections set forth in the Office Action have been overcome by amendment.

### **1. Objection to claims**

The Office Action states that claims 46 and 47 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicants address the rejection of claim 23 in section 2 below.

### **2. Rejection of claims 1, 23, 41, 42, 45-48, and 50-53 under 35 U.S.C. § 102**

The Office Action maintains a rejection of claims 1, 23, 41, 42, 45-48, and 50-53 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent Nos. 5,695,953 and 5,981,701 (the Wallach patents), which the Action asserts have an effective priority date of September 12, 1988. In particular, the Action maintains that the Wallach patents disclose the isolation of a TNF binding protein isolated from the urine of human patients, and that absent evidence to the contrary, this soluble TNF binding protein is identical to that of the protein of SEQ ID NO: 4 of the instant application. The Action also maintains that although the claims of the instant application recite a recombinant polypeptide, there is no evidence that a recombinantly produced polypeptide would differ from the protein purified from urine disclosed in the Wallach patents.

Applicants respectfully disagree with the Action's assertion that there is no evidence that the recombinantly produced polypeptide recited in claims 1, 23, and 41 would differ from the soluble TNF binding protein described in the Wallach patents. In fact, while the recombinantly produced polypeptide recited in claims 1, 23, and 41 would, by definition, constitute a single species, the evidence clearly indicates that as a result of the processing of the N-terminus of human urinary TNF *in vivo*, the human urinary TNF-BP taught by Wallach does *not* constitute a single species. In particular, the evidence indicates that Wallach and Applicants used substantially similar purification protocols, and that Applicants obtained a heterogeneous mixture of TNF-BP proteins from human

urine. With regard to the teachings of the instant specification, Applicants subjected highly purified samples of human urinary TNF-BP to SDS-PAGE, which "resulted in a diffuse band" (page 38, lines 8-9). The specification confirms that the "diffused appearance of the band" was "due to the presence of . . . a second polypeptide in a smaller amount" (page 38, lines 11-13). The second polypeptide "is longer than TNF-BP at the end terminus" and its sequence "coincides with the N-terminal secondary sequence . . . which is obviously split off from the processed protein" (page 38, lines 15-16, 19-20). Amino acid sequence analysis revealed that only 80% of purified TNF-BP begins with Asp-41 of SEQ ID NO: 4, while a secondary sequence beginning with Leu-30 of SEQ ID NO: 4 was also detected (page 39, lines 26-31). Clearly, the processing of residues 30-40 of SEQ ID NO: 4 *in vivo* is not wholly efficient and/or precise. Thus, TNF-BP purified from human urine is a mixture of at least two polypeptides whose N-terminus differs by 11 amino acids.

As described above, the purification protocol for human urinary TNF-BP described by Applicants in the specification is substantially similar to that taught by Wallach. In fact, Applicants' purification protocol incorporates the purification steps taught by Wallach, as well as an additional, highly specific purification step. Wallach teaches a purification process of TNF-BP involving dialysis and concentration of human urine, ion exchange chromatography, and reverse phase HPLC (U.S. Patent No. 5,981,701, col. 7-10). Similarly, Applicants' purification scheme involved dialysis and concentration of urine, ion exchange chromatography, and reverse phase FPLC (pages 36-38). Applicants, however, further purified TNF-BP by carrying out an additional, highly specific purification step of affinity chromatography using rTNF (page 36-37). Since Applicants teach an even more extensive purification scheme of TNF-BP than Wallach, the preparation of TNF-BP by Wallach almost certainly contained the contaminating, uncleaved species of TNF beginning with Leu-30 of SEQ ID NO: 4. Indeed, Wallach conceded that his preparation was "substantially purified" and that the "initial yield" from protein micro-sequence analysis was "over 40%, indicating that the major protein in the preparation (the 27 kDa band) is related to the resulting sequence" (U.S. Patent No. 5,981,701, col. 10, lines 6 and 17-20). Recombinant TNF-BP is not produced via processing of its N-terminus and will not contain contaminants beginning with Leu-30 of SEQ ID NO: 4. Applicants contend, therefore, that the recombinantly produced polypeptide recited in claims 1, 23, and 41 differs from the soluble TNF-BP preparation described in the Wallach patents.

Notwithstanding the clear differences between the recombinantly produced polypeptide

recited in claims 1, 23, and 41 and the soluble TNF-BP preparation described in the Wallach patents, Applicants have added new claims 54-56 in order to more particularly point out and distinctly claim the subject matter that Applicants regard as the invention. New claims 54(a)-(c), 55(a)-(c), and 56(a)-(c) specify that the polypeptide be expressed from a gene unaccompanied by nucleotide sequence encoding amino acid residues 1-29, 30-40, or 1-40 of SEQ ID NO: 2. The specification teaches that the processing of the N- and C-termini of human urinary TNF *in vivo* yields TNF-BP (page 20, lines 26-32). The first "29 amino acids constitute the signal peptide required for the secretion process, which is split off during secretion" (page 21, lines 31-33). Residues 30-40 correspond to the "N-terminal 11 amino acids" that "are split off from the processed protein at a later time by extracellular proteases" (page 22, lines 4-5). The recombinant form of TNF-BP claimed in 54(a)-(c), 55(a)-(c), and 56(a)-(c), however, is expressed from a gene that does not encode either residues 1-29 or 30-40 or both.

Applicants contend that the absence of the expressed leader sequences in the recombinant form of a TNF-BP is a valid distinction to overcome the Wallach patents. Due to the expression of the leader sequence of TNF, TNF-BP purified from human urine is a heterogeneous mixture of TNF-BP; recombinant TNF-BP expressed without the leader sequence does not contain such impurities. Furthermore, case law supports distinguishing naturally-occurring and recombinant polypeptides by leader sequence. In *Novo Nordisk of North America, Inc. v. Genentech, Inc.*, 77 F.3d 1364 (Fed. Cir. 1996), the Federal Circuit discusses claim 2 of U.S. Patent 4,601,980 ('980 patent), whereby Genentech distinguished recombinant human growth hormone (hGH) from hGH extracted from the pituitary glands of human cadavers by providing a method for "directly expressing" a human growth hormone expression product "*unaccompanied by the leader sequence* of human growth hormone." *Id.* at 1366, 1368 (emphasis added). Recombinant expression of hGH without the leader sequence was the essence of the invention. *Id.* at 1366. While not method claims, claims 54, 55, and 56 are analogous to claim 2 from the '980 patent in that the essence of both inventions is a polypeptide expressed without its leader sequence.

Similarly, new claims 54(d), 55(d), and 56(d) are limited to polypeptides expressed by a gene unaccompanied by nucleotides encoding residues 202-455 of SEQ ID NO: 2. The specification teaches that, in its natural synthesis, TNF-BP is obtained from a membrane-bound form of TNF by proteolytic cleavage just outside the transmembrane domain between Asn-172 and Val-183, which

corresponds to Asn-201 and Val-202 in SEQ ID NO: 2 (page 22, lines 6-9). Recombinant production of TNF-BP, however, allows for controlled expression that does not go beyond the C-terminal end of TNF-BP. As with the leader sequences of TNF, the proteolytic cleavage of the C-terminus is likely to be inefficient, resulting in polypeptides that do not end in Asn-172. Indeed, analysis of the amino acid composition of the C-terminus revealed small quantities of polypeptide ending in Glu-171 and Ile-170. Natural variations in the length of TNF-BP due to imprecise and/or inefficient processing provide compelling evidence that recombinant TNF-BP is distinct from natural TNF-BP. Therefore, absence of the C-terminal transmembrane and cytoplasmic regions of TNF in the expression of recombinant TNF-BP adequately distinguishes recombinant TNF-BP from human urinary TNF-BP. Applicants have also added new dependent claims 57-62, which include limitations on the source of the polypeptide (*i.e.*, prokaryotic or eukaryotic cells).

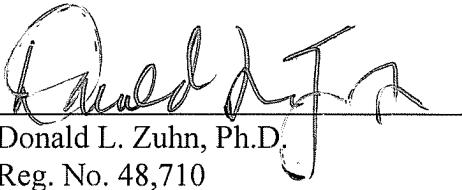
Applicants, therefore, respectfully request that the rejection of claims 1, 23, 41, 45-48, and 50-53 on 35 U.S.C. § 102 grounds be withdrawn.

### **CONCLUSIONS**

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. Allowance of the claims is thereby respectfully solicited.

If Examiner O'Hara believes it to be helpful, she is invited to contact the undersigned representative by telephone at 312-913-0001.

Respectfully submitted,  
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Dated: September 5, 2006